DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 17 2010

Rec'd 6/17/2010

Pankaj Dave, Ph.D.
Vice President, Regulatory Affairs
Navinta LLC
1499 Lower Ferry Road
Ewing, NJ 08618

Re: Docket No. FDA-2009-P-0601

Dear Dr. Dave:

This letter responds to your citizen petition, received on December 22, 2009 (Petition), requesting that the Food and Drug Administration (FDA or Agency) refrain from granting final approval for an abbreviated new drug application (ANDA) for a generic version of Naropin (ropivacaine hydrochloride (HCl) monohydrate) injection if the ANDA includes a section viii statement pursuant to section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 355(j)(2)(A)(viii)) with regard to U.S. Patent No. 5,670,524 (the '524 patent), unless that ANDA also includes a paragraph IV certification pursuant to section 505(j)(2)(A)(vii)(IV) of the Act to the drug substance and drug product claims in claims 9 and 10 of the '524 patent. Your petition recognizes one exception to this certification requirement, namely that any ANDA that was submitted to FDA before the '524 patent was listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) and that contained an appropriate patent certification at the time that patent was submitted for listing in the Orange Book is not required to certify to the '524 patent.

We have carefully considered the Petition.[1] For the reasons described below, the Petition is granted.

[1] You submitted a supplement to the Petition on February 19, 2010, to correct an error that had omitted the concluding words in a sentence in the Petition as received by us on December 22, 2009, and subsequently resubmitted this supplement with a verification statement on May 11, 2010. Upon correction, the last sentence on page 1 of the Petition reads as follows:

> Any ANDA that was submitted to FDA before the '524 patent was listed in the Orange Book and that contained an appropriate patent certification at the time that patent was submitted for Orange Book listing is outside the scope of this petition, as any such ANDA is not required to certify to the '524 patent by FDA's "late listing" regulation, 21 C.F.R. § 314.94(a)(12)(vi).

FDA-2009-P-0601

PAV

I. BACKGROUND

A. Naropin

Naropin (ropivacaine HCl monohydrate) injection was approved by FDA on September 24, 1996, and is sold in the United States at strengths of 2 milligrams/milliliter (mg/mL), 5 mg/mL, 7.5 mg/mL, and 10 mg/mL. AstraZeneca LP submitted the new drug application (NDA) 20-533 for Naropin (NDA 20-533). APP Pharmaceuticals, LLC (APP) is the current holder of NDA 20-533. Naropin is indicated for the production of local or regional anesthesia for surgery and for acute pain management.

B. The '524 Patent

The '524 patent entitled "Methods and Compositions for the Treatment of Pain Utilizing Ropivacaine" issued on September 23, 1997, but was not submitted for listing in the Orange Book by the NDA holder within 30 days of its issuance. The '524 patent was submitted by the NDA holder on November 15, 2007, received by FDA on November 16, 2007, and subsequently listed in the Orange Book on November 27, 2007.[2] The '524 patent as it appears in the Orange Book is assigned use code U-833, "method of treating pain using a pharmaceutically acceptable salt of ropivacaine and administering a composition containing less than 0.25% by weight of ropivacaine." The '524 patent is also flagged as containing relevant drug substance claims and drug product (composition) claims.

C. Navinta's ANDA

According to Navinta, the relevant facts are as follows. Navinta is the applicant for ANDA 78-601 for a generic version of Naropin (5 mg/mL, and 10 mg/mL strengths).[3] Navinta's ANDA was physically received by FDA on November 13, 2006, and included a paragraph IV certification to U.S. Patent No. 4,870,086 (the '086 patent). At the time Navinta's ANDA was received, the '086 patent was the only patent listed in the Orange Book in connection with Naropin. As initially submitted, Navinta's ANDA sought approval for both surgical anesthesia and acute pain management. After the '524 patent was listed by APP in the Orange Book, Navinta amended its pending ANDA to seek approval for a generic product with "carved out" labeling that included only the anesthesia indication, and omitted from the proposed labeling the acute pain management indication protected by the '524 patent.

D. Statutory and Regulatory Requirements

The Act and FDA regulations require that an entity seeking to market a new drug to submit an NDA or ANDA. NDAs contain, among other things, extensive scientific data

[2] The '524 patent first appeared in the November 2007 monthly supplement to the Orange Book with an "add" notation.

[3] According to the petition, ANDA 78-601 as originally submitted included the 2 mg/mL strength. This strength was subsequently withdrawn by Navinta.

demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that an applicant of an NDA submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act requires NDA applicants to file as part of the NDA:

> the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.[4]

FDA is required to publish certain patent information for patents claiming drugs approved under section 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) of the Act is known as a *listed drug*.[5] Under provisions added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling) and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail in section I.D.1., the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[6] In general, an ANDA may not

---

[4] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

[5] Under 21 CFR 314.3(b), "[*l*]*isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified in the Orange Book as having an effective approval.

[6] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Marketing exclusivity for the listed drug is not at issue here.

obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights.

1. Paragraph I-IV Certification

With respect to each patent that claims a listed drug and is submitted by the NDA applicant for listing in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) That the required patent information relating to such patent has not been filed (paragraph I certification)
(II) That such patent has expired (paragraph II certification)
(III) That the patent will expire on a particular date (paragraph III certification)
(IV) That such patent is invalid or will not be infringed by the drug for which approval is being sought (paragraph IV certification)

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing.

Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

As a reward for challenging a patent and potentially clearing the way for generic competition, the first ANDA applicant who submits a paragraph IV certification to a patent is eligible for 180 days of marketing exclusivity. When an ANDA applicant with a paragraph IV certification is eligible for this exclusivity, the exclusivity generally prohibits FDA from approving any subsequent ANDA with a paragraph IV certification to that patent before the triggering of and during the exclusivity period (section 505(j)(5)(B)(iii)-(iv) of the Act (2002)).[7]

2. Section viii Statement

The paragraph I, II, III, and IV certifications are not the only manner in which an ANDA applicant may address all relevant patents. When a patent is listed only for a method of use, an ANDA applicant seeking to omit from its labeling that approved method of use covered by the listed patent need not file a paragraph I to IV certification for that patent. Instead, the applicant may submit a *section viii* statement acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides the following:

> if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use.

If an ANDA applicant submits such a statement, that applicant must omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)).[8] If an ANDA applicant files a section viii statement to a patent that protects only a method of use (and makes the requisite labeling carve out), the patent

---

[7] Congress amended section 505(j) of the Act in late 2003 (see the Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (MMA) (Dec. 8, 2003)). The majority of the amendments pertaining to 180-day exclusivity do not apply to the exclusivity determinations for the Naropin ANDA, because the earliest ANDA containing a paragraph IV certification was submitted before the December 8, 2003, enactment date of the MMA.

[8] See also H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

claiming the protected method of use will not serve as a barrier to ANDA approval nor will 180-day exclusivity with respect to that patent serve as such a barrier.

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement as follows:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.

Accordingly, FDA regulations also expressly recognize that an application that does not seek approval for a condition of use claimed by a listed patent may omit that condition of use from its labeling by submitting a section viii statement.[9]

Section 505(j)(2)(A)(viii) of the Act and the implementing FDA regulations (§ 314.94(a)(12)(iii)) allow a section viii statement only for patent claims that describe a method of use. Thus, where a patent is submitted and is represented to include both method-of-use and other claims that claim the approved drug product (such as drug product and/or drug substance claims), the section viii statement would be inapplicable to the other patent claims. For drug product claims, an ANDA applicant would be required to submit the appropriate certification under section 505(j)(2)(A)(vii) of the Act. Therefore, under the Act, a section viii statement alone would be insufficient to meet the statutory patent certification requirement where the NDA holder submitted an acceptable patent declaration that requested that FDA list the patent as including drug product claims that claim the approved drug product in addition to method-of-use claims.

The Agency has previously explained that a paragraph IV certification and a section viii statement "are not overlapping, and an applicant does not have the option of making a certification under § 314.94(a)(12)(i)(A)(*4*) in lieu of, or in addition to, a statement under § 314.94(a)(12)(iii)" (see FDA, Final Rule, Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions (59 FR 50338 at 50347 (October 3, 1994)). The Agency further noted (59 FR 50338 at 50347):

> If, however, there are listed patents that present both a product and method of use claim, the applicant may file a paragraph IV certification with respect to the product patent or patent claim and a statement that the product that is the subject of the application does not involve a patented method of use with respect to the method of use patent or patent claim.

[9] Such an applicant must demonstrate that the differences in labeling render its proposed drug product no less safe and effective than its listed drug for the remaining, nonprotected conditions of use (21 CFR 314.127(a)(7)).

Thus, where a patent is submitted as claiming both the approved drug product and an approved method of using the drug, if an ANDA applicant does not seek approval for the method of use claimed by the patent but seeks approval of the drug product for a different use before the patent expires, FDA's practice is to allow a *split* certification to that patent, which includes both a paragraph IV certification to the drug product claim and a section viii statement to the method of use and an accompanying labeling carve out. When a patent is listed with multiple method-of-use claims, FDA permits an ANDA applicant to submit a split certification with a paragraph IV certification to a method of use for which the applicant seeks approval and a section viii statement for a method of use the applicant seeks to carve out from its labeling. In either case, the ANDA applicant must address all claims for which the patent was submitted and may file a paragraph IV certification to some claims and a section viii statement to other claims, as appropriate (see Repaglinide Citizen Petition Response, Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 (December 4, 2008) (Repaglinide Petition Response) at 18). This approach preserves the NDA holder's statutory right to defend its patent rights prior to ANDA approval while permitting the ANDA applicant to exercise its statutory right to seek approval for fewer than all of the approved conditions of use.

3. Late-Listed Patents

Timely filing of patent information by the NDA applicant is crucial to the success of the statutory scheme created by the Hatch-Waxman Amendments. Filing of patent information triggers the listing in the Orange Book, which provides notice to a potential ANDA applicant of the patents that may protect the innovator drug product, thus allowing the ANDA applicant to provide the appropriate certification under section 505(j)(2)(A)(vii) of the Act. The statutory requirement that patent information be submitted with the NDA, by amendment prior to approval of the NDA, or within 30 days after the patent issues (section 505(b)(1) and (c)(2) of the Act) shows that Congress intended timely submission of patent information. If patents could be submitted for listing at any time after issuance and ANDA applicants with pending applications were required to certify regardless of the lateness of the listing, the NDA holder would have an incentive to delay the patent listing, (and, thus, delay the commencement of patent litigation and potentially delay ANDA approval or marketing), thereby extending its monopoly.

FDA's implementing "late-listing" regulation in § 314.94(a)(12)(vi) was intended to enforce timely submission of patent information. The regulation states that:

> If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification.
>
> An applicant whose abbreviated new drug application is submitted after a late submission of patent information, or whose pending abbreviated

application was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, shall submit a certification under paragraph (a)(12)(i) of this section or a statement under paragraph (a)(12)(iii) of this section as to that patent.

The Agency believes that this approach best embodies the compromise adopted by Congress which protects the patent rights of innovators while encouraging prompt and efficient entry of generics onto the market (59 FR 50338 at 50340). Thus, if an NDA applicant submits required patent information on an approved drug product more than 30 days after issuance of the patent, FDA will publish the untimely information, but will not require ANDA and 505(b)(2) applicants with pending applications that contain an appropriate certification, i.e. those applicants who would be prejudiced by the late submission, to recertify to the new patent. Only applicants who initially submit ANDAs or 505(b)(2) applications after the submission of the patent information or whose pending applications do not contain an appropriate certification at the time the patent information is submitted would be required to submit a certification as to that patent. The Agency noted (59 FR 50338 at 50340) that "this approach is the best means for discouraging manipulation of the patent filing scheme and providing optimum notice of applicable patents" (59 FR 50338 at 50340).

II. ANALYSIS

In the Petition, you assert that the '524 patent was not listed in FDA's Orange Book until more than ten years after it issued (Petition at 4). You assert that although ANDAs that were pending at the time of the "late listing" of the '524 patent are not required to certify to that patent, for ANDAs submitted after the "late listing" of the '524 patent, certification is required. Specifically, you assert that if an ANDA that was submitted after the '524 patent submission seeks approval for proposed labeling that carves out Naropin's acute pain management indication and includes an accompanying section viii statement to the method-of-use claims in the '524 patent, FDA must require that the ANDA applicant also submit a paragraph IV certification to the drug substance and drug product (composition) claims of the '524 patent and give notice of that certification to APP (Petition at 6). You state that if an ANDA applicant whose ANDA was submitted after the patent was submitted for listing is permitted to submit or maintain a section viii statement with regard to the '524 patent, without also submitting a paragraph IV certification to the drug substance and drug product claims of that patent, that applicant would derive an unfair competitive advantage vis-à-vis Navinta (Petition at 9).[10]

[10] Specifically, you state that such an ANDA applicant might submit a paragraph III certification to the '086 patent (thereby indicating it does not seek final ANDA approval before expiration of that patent on September 24, 2010), and seek to carve out the method of use claims in the '524 patent by means of a section viii statement to the '524 patent (Petition at 7-8). You thus state that by virtue of having no Paragraph IV certification in its ANDA, such an applicant would not have to give notice to APP of its pending ANDA, would not face the possibility of a patent suit and would, thus, receive an unfair competitive advantage vis-à-vis Navinta (Petition at 7-8).

FDA's role in listing patents and patent information in the Orange Book is ministerial (see *American Bioscience v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001)). FDA relies on the NDA applicant to provide an accurate patent submission. In keeping with our practice of relying solely on the NDA applicant's patent declaration describing relevant patent claims in Orange Book-listed patents, we will rely on the patent declarations submitted to FDA regarding the '524 patent, in which the NDA applicant has indicated that this patent contains drug substance and drug product claims that claim the approved drug product in addition to method-of-use claims that claim an approved method of using such drug product.

As noted above in section I.D.2, the scope of a section viii statement is limited to patent claims that describe an approved method of use. As confirmed by FDA in the Repaglinide Petition Response, if the patent is listed as containing both relevant method-of-use and relevant drug product claims, an ANDA applicant who is required to certify who submits a section viii statement for the method-of-use claims must also submit an appropriate certification under section 505(j)(2)(A)(vii) of the Act for any drug product claims (Repaglinide Petition Response at 18). Thus, if an ANDA applicant does not seek approval for the method of use claimed by such a patent (but seeks approval of the drug product before the patent expires), FDA's practice is to allow a split certification to that patent, which includes both a certification under section 505(j)(2)(A)(vii) of the Act to the drug substance or drug product claim and a section viii statement to the method of use claim.

Consistent with the late-listing regulation, an applicant whose ANDA is submitted after a late submission of patent information, or whose pending ANDA was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, must certify to the late-listed patent as described above. Thus, any ANDA submitted after the '524 patent was submitted for listing in the Orange Book must include an appropriate certification under section 505(j)(2)(A)(vii) of the Act for the drug product and drug substance claims even if the applicant seeks to carve out the method of use claimed by the patent. The submission of only a section viii statement for the method-of-use claims without an appropriate certification for the drug product and drug substance claims would not meet the requirements of the Act or FDA's regulations.

Although Navinta discusses its approach to addressing the '524 patent, which was late-listed with respect to Navinta's ANDA, the Petition does not request any action from FDA with respect to Navinta's ANDA, or any other similarly situated ANDA. As stated in the Petition, such similarly situated ANDAs are outside the scope of the Petition. Therefore, this response need not address certification obligations of Navinta, or any other similarly situated ANDA applicant.

III. CONCLUSION

For the reasons stated above, the Petition is granted regarding any ANDA submitted after the late submission of the '524 patent, or any pending ANDA submitted before the late submission of the '524 patent, but not containing an appropriate patent certification at the time the '524 patent was submitted.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research